DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: MAR 1 2005

From: Consumer Safety Officer, Division of Dietary Supplement Programs , Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: CREATINE FROM CREATINE ETHYL ESTER HCL (CE2)

Firm: MEDICAL RESEARCH INSTITUTE

Date Received by FDA: DECEMBER 1, 2004

90-Day Date: MARCH 1, 2005

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Victoria Lutwak

19955-0316

RPT264

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January 25, 2005

Via Federal Express

Office of Nutritional Products, Labeling,
And Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740-3835

Re: New Dietary Ingredient Notification: Creatine

Dear Sir or Madam:

It has come to our attention that we failed to include the October 20, 2004 correspondence to Linda S. Pellicore, Ph.D. that was discussed in Section Six, page 3, of our submission. For that reason, we are including an original and two copies of a revised Section Six, Table of Contents, and additional Attachment 27, which includes the October 20, 2004 correspondence to Linda S. Pellicore, Ph.D.

Sincerely,

W. Patrick Noonan

WPN:mw
Enclosures

TABLE OF CONTENTS

SECTION SIX - History of use or other evidence of safety establishing that the dietary ingredient creatine from creatine ethyl ester HCL as recommended in the labeling of dietary supplement products will be reasonably expected to be safe.

Attachment 6 - Vennerstom JL, Miller DW. Creatine Ester Pronutrient Compounds and Formulations. International publication number WO 02/221535A1. World Intellectual Property Organization, 21 March 2002.

Attachment 7 – Ferro Pfanstiehl. Computer printout of A History of Innovation.

Attachment 8 – "Creatine Fuel" and "Creatine 1000" trademark applications with filing dates.

Attachment 9 - Kreider RB. Creatine Supplementation: analysis of ergogenic value, medical safety and concerns. *JEPonline* 1:1, 1998.

Attachment 10 - Anonymous. Long term safety of oral creatine supplementation, Fact Sheet No. 4. Provided by Creapure® manufacturer Degussa BioActives.

Attachment 11 - Poortmans Jr, Francaux M. Adverse effects of creatine supplementation: Fact or Fiction? *Sports Med* 30: 155-170.

Attachment 12 - Shilling, BK, Stone MH, *et al*. Creatine supplementation and health variables: A retrospective study. *Med Sci Sports Exerc* 33: 183-188, 2001.

Attachment 13 - Dietary Supplements: Toxicology and Clinical Pharmacology edited by M.J. Cupp and T.S. Tracy. Humana Press, Creatine Monohydrate pp. 91-120.

Attachment 14 - Persky, AM, Brazeau, G. Clinical Pharmacology of the Dietary Supplement Creatine Monohydrate. *Pharmacological Reviews*, May 10, 2001.

Attachment 15 - Kreider, RB. Effects of creatine supplementation on performance and training applications. *Molecular and Cellular Biochemistry* 244: 89-94, 2003.

Attachment 16 - Robinson TM, Sewell DA, *et al.* Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function. *Br J Sports Med* 34: 284-288, 2000.

SECTION SIX

The history of use or other evidence of safety establishing that the dietary ingredient creatine from creatine ethyl ester HCl when used under the conditions recommended or suggested in the labeling of dietary supplement products will reasonably be expected to be safe and which is the basis on which the distributor of creatine from creatine ethyl ester HCl has determined that the use of creatine from creatine ethyl ester HCl is reasonably expected to be safe. See 21 CFR Section 190.6(b)(4).

INTRODUCTION

Creatine ethyl ester HCl as the source of creatine is a structurally related chemical analog of creatine. The difference between creatine and creatine ethyl ester HCl is that the carboxylic acid group of creatine has been masked through the formation of an ester linkage. The masking of the carboxylic acid, results in a creatine-based compound with both increased aqueous solubility and enhanced membrane partitioning compared to standard creatine monohydrate. (See Vennerstom JL, Miller DW. Creatine Ester Pronutrient Compounds and Formulations. International publication number WO 02/221535A1. World Intellectual Property Organization, 21 March 2002, as Attachment 6.)

Creatine has been available to retail consumers as a dietary supplement from various sources since 1992 and would be a "grandfathered" dietary ingredient under Section 413(c) of the FDC Act. From initial marketing until now, no significant health concerns have been identified in either controlled human studies, or acute and sub-acute toxicity studies in laboratory animals. Creatine ethyl ester HCl is a combination of creatine and ethanol which has been shown in ChemPharma laboratory study (see Attachment 24) to enter the body following oral administration as the individual constituents creatine and ethanol (i.e. ethyl alcohol) Ethyl Alcohol is listed in the "Food Chemicals Codex" 4th ed. (1996 p136) and is affirmed as GRAS by FDA at 21 CFR Section 184.1293 as an ingredient used "as an antimicrobial agent . . . not to exceed 2.0 percent by product weight." It is also subject to a food additive regulation at 21 CFR Section 169.175 as component of vanilla extract.

Additionally, Triethyl citrate found at 21 CFR Section 184.1911 is the triethyl ester of citric acid. It is prepared by esterifying citric acid with ethyl

alcohol. FDA also recognizes the dietary supplement status of botanical extracts in ethanol. See 21 CFR Section 101.36(b)(3)(ii)(B).

Attachments 7 and 8 indicate creatine was produced for sale by Pfanstiehl laboratories as early as 1972 and was subject to trademark applications by marketing companies in 1993 that allege existing commercial use in commerce of creatine. Based on that prior commercial use, creatine could be considered a "grandfathered dietary ingredient" under Section 413(c) of the FDC Act. Additionally, ethyl alcohol is GRAS and a component of approved food additives. For that reason, we would conclude that the amino acid creatine from the source product of both creatine and ethyl alcohol (i.e. creatine ethyl ester) would clearly meet the definition of a dietary supplement found at Section 201 (ff)(D)(E) of the FDC Act.

Safety of Creatine from Creatine Ethyl Ester HCl

Numerous studies evaluating the relative safety of creatine supplementation for healthy adults have been published. (See Attachments 9-15.) These human studies include both short and long term studies, and have established that dietary supplementation with creatine is not associated with any adverse health effects. No differences were noted in serum markers of liver or kidney function between groups using creatine supplementation as compared to placebo. (See Attachments 16-19.) Two case reports of kidney dysfunction following creatine use exist within the medical literature. However, neither case report was able to demonstrate a causative relationship with creatine supplement use. (See Attachments 20 and 21.) Creatine is an accepted ergogenic supplement in all major athletic organizations, including IOC, NCAA and other major sports organizations. (See Attachments 22 and 23.)

Ethanol is a well-established component of the human diet. The supplementation of a daily dosage of creatine from creatine ethyl ester of 5 grams contains 1.47 grams of ethanol. A single cocktail made with 40 proof liquor contains as a matter of comparison to regular human use contains 16.8 grams of ethanol. This normal human use is more that 10 times the amount of ethanol provided in the recommended daily dosage of creatine from creatine ethyl ester HCl.

Results reported in the September 2002 75 day premarket notification by PNT indicated that in a long term human trial involving five subjects, that there was one subject with a slightly elevated serum creatinine level (1.7 mg/dl), whereas normal levels are typically 0.8-1.5

mg/dl. This matter was cited by FDA as one concern regarding the position that creatine ethyl ester is reasonably expected to be safe. The elevated creatinine level mentioned above is only 13% above the normal range, and given the limited number of subjects and the nature of the analytical methodology, it is arguable this finding would not represent a clinically significant increase or cause for concern. Additionally, it has been established in this 75 day premarket notification that the safety of creatine and ethanol is the relevant issue because both constituents will result in the body under normal recommended use of creatine from creatine ethyl ester HCl.